## REMARKS

Status of the Claims

*Pending claims*

Claims 1, 2, 5, 6, 11 to 16, 29, 47 to 92, 95 to 107, 111 to 115, and 117 to 124 are pending. Claims 49 to 73, 95 to 100, 107, 111 to 115 and 117 to 122 are withdrawn from consideration. Accordingly, claims 1, 2, 5, 6, 11 to 16, 29, 47, 48, 74 to 92, 101 to 106, 123 and 124 are pending and under consideration.

*Claims added and canceled in the Instant Response*

Claims 13, 14, 76 to 86, 89 to 92, 123 and 124 are canceled, without prejudice, and claims 125 to 132 are added. Thus, after entry of the instant amendment, claims 1, 2, 5, 6, 11, 12, 15, 16, 29, 47, 48, 74, 75, 87, 88, 101 to 106, and 125 to 132, will be pending and under consideration.

*Outstanding Rejections*

Claims 1, 5, 6, 11 to 16, 29, 47, 48, 74 to 92, 101 to 106, 123 and 124 stand rejected under 35 U.S.C. §112, first paragraph, enablement requirement; please see the paragraph spanning pages 3 and 4, to line 4 of page 7, of the instant office action (the OA). Claims 1, 15, 16, 29, 47, 48, 74 to 91, 101 to 106, 123 and 124 stand rejected under 35 U.S.C. §112, first paragraph, written description requirement; please see page 7, line 5 (first full paragraph) to page 9, line 16, of the OA. Claims 1, 2, 11, 15 to 16, 29, 47, 48, 74 to 83, 86, 92, 101 to 106 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachibana, et al., J. Ferment. Bioeng. 1996, vol. 82(3):224-232; GenBank Accession No. O33476, Jan. 1998 ("Tachibana").

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims directed nucleic acids having various sequence

identities to exemplary sequence of the invention, e.g., at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 93%, 95%, 96%, 97%, 98% or 99% sequence identity, which includes 93% or 97% sequence identity, can be found, inter alia, on page 5, paragraph 0015; page 16, paragraph [0068]; page 19, paragraph [0076]; page 61, paragraph [212]; pages 65 to 66, paragraphs [0226] and [0227].

The Restriction Requirement, Election and Traversal

The Patent Office alleged that the pending claims of the application are directed to nineteen (XIX) separate and distinct inventions under 35 U.S.C. §121. In response, Applicants elected Group I, claims 1 to 29, 47, 48, 74 to 92 and 101 to 106, drawn to polynucleotides, vectors, host cells comprising same, probes for same and a method of making a polypeptide using the polynucleotides of the invention, with traverse, giving reasons to reconsider and withdraw the restriction requirement. Applicants noted that after the elected product claims have been found to be allowable, the withdrawn process (methods) claims of Groups IV, VII, VIII, IX, XI, XIII, XIV, XV, XVI, XVIII and XIX should be rejoined. MPEP §821.04; pg 800-63, 8th Edition, August 2001; In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995); In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1995); 1184 OG 86, 3/26/96.

Supplemental Information Disclosure Statements

Applicants thank the Examiner for considering and initialing the non-patent literature listed on the Supplemental Information Disclosure Statements (IDSs) submitted on April 11, 2005, and March 10, 2005. It is respectfully requested that the cited information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

Issues under 35 U.S.C. §112, first paragraph

Enablement

Claims 1, 5, 6, 11 to 16, 29, 47, 48, 74 to 92, 101 to 106, 123 and 124 stand rejected under 35 U.S.C. §112, first paragraph, enablement requirement, as allegedly not described in the

specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The Patent Office acknowledged that the specification enables a polynucleotide SEQ ID NO:1 encoding an enzyme SEQ ID NO:2, having amylase activity.

However, the Patent Office alleges that the specification does not provide reasonable enablement for the claimed genus of polynucleotides, including nucleic acids having 70%, 75%, 80%, 85%, 90% or 95% sequence identity to SEQ ID NO:1.

The Office notes it is concerned about the size of the claimed genus of nucleic acids used in the compositions and methods of the invention (see page 5, lines 9 to 11, and page 6, lines 18 to 22, of the OA). The instant amendment to the claimed invention addresses the Office's concerns about the size of the genus. For example, amended claim 1 is directed to nucleic acids comprising, inter alia, sequences having at least 90% sequence identity to SEQ ID NO:1. Amended claim 2 is directed to nucleic acids comprising, inter alia, sequences that hybridize under specific conditions of high stringency to SEQ ID NO:1, and having at least 90% sequence identity to a sequence as set forth in SEQ ID NO:1. Amended claim 29 is directed to nucleic acids comprising, inter alia, sequences encoding a polypeptide having an amino acid sequence having at least about 95% sequence identity to a sequence as set forth in SEQ ID NO:2.

The Patent Office alleged that because the claimed genera are very large guidance must be provided to determine which changes can be tolerated in a protein's amino acid sequence to obtain a desired activity to practice the invention without undue experimentation (see, e.g., page 5, lines 9 to 15, and page 6, lines 9 to 17).

Applicants respectfully aver that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, a genus of nucleic acids encoding polypeptides having amylase activity to practice the claimed invention – and will provide evidence and expert declaration to support this argument.

However, Applicants respectfully aver that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and as specifically addressed, below, how the art used to support the Office's enablement rejection is not sufficient to rebut the presumptively enabled specification.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, 8th ed., rev. 2, May 2004, pg 2100-189.

The Patent Office cited art to support its *prima facie* case of lack of enablement, where the cited art, Ngo, et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al. (Ed.) ("Ngo"), allegedly supports the unpredictability of the art in predicting function from a polypeptide primary structure. However, the relevant issue regarding enablement is not whether one can predict function from a polypeptide primary structure, but rather whether it would take undue experimentation to screen/ test for enzyme activity after making any particular amino acid residue change (how to make the many possible variants is not an issue).

Ngo was cited for allegedly supporting the unpredictability of the art by teaching that the relationship between the sequence of a peptide, its (tertiary) structure and its activity are not predictable. However, this reference is not sufficient to rebut the presumption of enablement. Ngo is not directed to whether, or not, making and screening a large number of nucleic acid and polypeptide variants would have constituted undue experimentation to one skilled in the art at the time of the invention (the relevant issue). Ngo does not support unpredictability in the art, but rather teaches that one of skill in the art could easily target a minimum number of residues to predictably generate a limited number of enzyme variants.

Ngo is a review chapter from a 1994 publication that opines that, at least as of 1994[1], there was no efficient algorithm for accurately predicting the structure of a given protein from its amino acid sequence alone. In fact, Ngo's data suggested that most changes in a polypeptide's amino acid sequence (e.g., non-binding or non-catalytic site amino acid residues) are not important in determining, or changing, binding or catalytic specificity. Thus, Ngo actually supports the idea that most changes in a polypeptide's amino acid sequence will result in little or no effect on its specificity or activity, and that one of skill in the art could easily target a minimum number of residues to predictably generate a limited number of nucleic acid variants to generate desired active (enzyme) variants. Thus, the Office has provided insufficient reasons why one of ordinary skill in the art would not have had a reasonable expectation of success in identifying the genus of amylases of the invention or the nucleic acids encoding them. In fact, it may be desirable for a polypeptide of the invention to have an activity that differs from that of the exemplary amylases of the invention.

The Office alleged, inter alia, that without specific guidance as to what regions of polypeptide structure could be modified without changing its activity or the general tolerance of the enzyme to sequence changes the size of the genus to be screened for activity would have been undue experimentation (see, e.g., page 6, lines 9 to 17, of the OA). In other words, it was alleged that is was not routine in the art to screen large numbers of polypeptides (equivalent to the size of the claimed genus) for amylase activity. However, as supported by Dr. Jay Short's declaration (see

attached Rule 132 declaration), the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art for screening polypeptides for amylase activity was very high. Dr. Short declares that procedures for making amylase enzyme fragments and sequence variations, e.g., with substitutions, deletions, insertions, and additions, were routine in the art at the time of the invention. He declares that assays for identifying amylase enzyme fragments were conventional and routine in the art at the time of the invention. Dr. Short declares that assays for identifying variant polypeptides having amylase activity were conventional and routine in the art at the time of the invention. For example, assays for identifying polypeptides having amylase activity are described in the specification, e.g., on pages 98 to 99 (in Example 5) of the specification, e.g., using FITC-starch in a 384-well plate (page 99, lines 13 to 18). Furthermore, Dr. Short declares that amylase activity assays also were well known in the art at the time of the invention, e.g., as described in USPNs 4,762,917 and 5,319,076 (describing modified oligosaccharide derivatives useful as substrates for measuring amylase activity and activity assays using same); 5,188,956; 5,366,883; 5,370,997; 5,578,479; 5,753,460, to list only a few examples. Dr. Short declares that many of these assays could have been adapted and used in high-throughput screening assays, which were well known in the art at the time of the invention. Dr. Short declares that using the teaching of the specification one of ordinary skill in the art would have been able to routinely make and use the claimed genus of nucleic acids and polypeptides without undue experimentation.

Furthermore, Applicants respectfully submit and Dr. Short declares that it would not have been necessary for the skilled artisan to understand which regions of the amylases of the invention could be modified to gain or change a function or activity, or be modified without loss of a function or activity. Dr. Short declares that it would not have been necessary for the skilled artisan to understand which specific regions of the amylase sequence or structure needed to be modified without affecting function or activity to routinely generate the genus of nucleic acids and polypeptides of the invention. Dr. Short declares that methods for making and screening sequence modifications and enzyme fragments were sufficiently comprehensive, routine and predictable at

[1] Considering the rapid advances in this field, Ngo's 1994 teaching is clearly not representative of the state of the art in protein structure predictive algorithms at the time of the instant invention (having a priority document filed February, 2001).

the time of the invention to predictably generate amylase-encoding sequences without need of knowing which specific regions of a sequence or structure affected function or activity. Dr. Short declares that methods known at the time of the invention for modifying nucleic acid and polypeptide sequences in combination with high through-put enzyme (amylase) screening made methods that required previous knowledge of what regions of polypeptide structure could be modified without losing activity obsolete and unnecessary[2].

Whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation -- time and difficulty are not determinative of undue experimentation if the experimentation is routine. See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); In re Wands, 858 F.2d at 736-40, 8 USPQ2d at 1403-7; Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) (acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."). Thus, enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit.

Analogously, practitioners of the biological sciences for the instant invention also recognize the need to screen numbers of negatives to find a sample that has the desired properties, e.g., amylase-encoding activity. As declared by Dr. Short, screening procedures – including high throughput assays – that could have been used to identify the genus of nucleic acids of the invention, including identifying nucleic acids encoding amylase activity under various conditions, were well known in the art and at the time the application was filed. These procedures comprised

[2] In one aspect, producing an amylase with an activity different from that of the exemplary SEQ ID NO:2 could very likely be a desired goal in practicing the instant invention.

routine protocols for the skilled artisan. Thus, the specification did provide the skilled artisan using Applicants' written disclosure a rational and predictable scheme for modifying amino acid residues in an amylase with an expectation of obtaining a desired biological function. Accordingly, the one of skill in the art at the time of the invention using Applicants' written disclosure could have practiced the instant claimed invention without undue experimentation.

Furthermore, Applicants respectfully aver that, if desired, direction and guidance to the skilled artisan as to which amino acid residue could have been modified to obtain a structural or functional amylase variant was also readily available in the art at the time of the invention. While not necessary, but if desired, one skilled in the art at the time of the invention had many sources of guidance, in addition to the specification, to determine which bases (amino acid residues) of a sequence of the invention could be modified to make, identify, screen for and use structural and/or functional variants of an exemplary amylases and nucleic acids of the invention without undue experimentation. For example, the three dimension structure of amylases had been described, see, e.g., Pereira (1999) "Specific inhibition of insect alpha-amylases: yellow meal worm alpha-amylase in complex with the amaranth alpha-amylase inhibitor at 2.0 A resolution" Structure Fold Des. 7(9):1079-1088; Hwang (1997) "Crystal structure of thermostable alpha-amylase from *Bacillus licheniformis* refined at 1.7 A resolution" Mol. Cells 7(2):251-258; Machius (1995) "Crystal structure of calcium-depleted *Bacillus licheniformis* alpha-amylase at 2.2 A resolution" J. Mol. Biol. 246(4):545-549; Kadziola (1994) "Crystal and molecular structure of barley alpha-amylase" J. Mol. Biol. 239:104-121, thus providing direction as to which amino acid residues can be modified and how structure correlates with function. Furthermore, at the time of the invention one of skill in the art would have been aware of the many studies of amylase activity, active sites and active site and enzyme structure, see, e.g., Kandra (2000) "Examination of the active sites of human salivary alpha-amylase (HSA)" Carbohydr. Res. 329(3):579-585; Brayer (2000) "Subsite mapping of the human pancreatic alpha-amylase active site through structural, kinetic, and mutagenesis techniques" Biochemistry 39(16):4778-4791; Ma (2000) "Removal of the four C-terminal glycine-rich repeats enhances the thermostability and substrate binding affinity of barley beta-amylase" Biochemistry 39(44):13350-13355; Kim (1997) "Crystal structure of a maltogenic amylase provides insights into a catalytic versatility" J. Biol. Chem. 274:26279-26286; Qian (1997) "Structure of a pancreatic

alpha-amylase bound to a substrate analogue at 2.03 A resolution" Protein Sci. 6:2285-2296;Oda (1997) Tertiary and quaternary structures of 0.19 alpha-amylase inhibitor from wheat kernel determined by X-ray analysis at 2.06 A resolution" Biochemistry 36:13503-13511; Matsui (1994) Biochemistry 33(2):451-458, "Roles of the aromatic residues conserved in the active center of *Saccharomycopsis* alpha-amylase for transglycosylation and hydrolysis activity;" Matsui (1991) Biochim. Biophys. Acta. 1077(3):416-419, "An increase in the transglycosylation activity of *Saccharomycopsis* alpha-amylase altered by site-directed mutagenesis", to name only a few. Accordingly, one skilled in the art at the time of the invention, using the teaching of the specification had many sources of direction to determine which amino acid residues could be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an amylase.

Accordingly, while not necessary, but if desired, one skilled in the art at the time of the invention had many sources of guidance, in addition to the specification, to start from an exemplary nucleic acid or polypeptide of the invention and determine which nucleic acids/ amino acid residues could be modified, substituted, deleted or inserted into a sequence to make and identify structural and/or functional variants of the claimed genus without undue experimentation. Thus, if desired, the skilled artisan had sufficient guidance to determine which changes could be tolerated in a protein's amino acid sequence to obtain a desired activity to practice the invention without undue experimentation.

In light of these remarks and the declaration and evidence provided herein, Applicants respectfully submit that the pending claims are fully enabled by the specification to meet the requirements of 35 U.S.C. §112, first paragraph.

Written Description

Claims 1, 15, 16, 29, 47, 48, 74 to 91, 101 to 106, 123 and 124 stand rejected under 35 U.S.C. §112, first paragraph, written description requirement; please see page 7, line 5 (first full paragraph) to page 9, line 16, of the OA.

*Genus encompassing 70% sequence identity*

Claims 29 and 74 to 91 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention. The Office notes it is concerned about the size of the claimed genus of nucleic acids used in the compositions and methods of the invention (see page 7, lines 5 to 21, of the OA) – i.e., a genus encompassing 70% sequence identity to SEQ ID NO:1. The instant amendment to the claimed invention addresses the Office's concerns about the size of the genus. For example, amended claim 29 is directed to nucleic acids comprising, inter alia, sequences encoding a polypeptide having an amino acid sequence having at least about 95% sequence identity to a sequence as set forth in SEQ ID NO:2. Amended claim 74 is drawn to nucleic acid probe comprising a polynucleotide as set forth in claim 1 or claim 2, which are directed to, inter alia, nucleic acids comprising sequences having at least 90% sequence identity to the exemplary SEQ ID NO:1.

*Genus encompassing 70% sequence identity over a region of 100 residues*

Claims 1, 15, 16, 29, 47, 48, 101 to 106 and 123 and 124 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention. The Office notes it is concerned about the size of the claimed genus of nucleic acids used in the compositions and methods of the invention (see page 8, line 1, to page 9, line 17, of the OA) – i.e., a genus encompassing 70% sequence identity over a region of 100 residues of SEQ ID NO:1. The instant amendment to the claimed invention addresses the Office's concerns about the size of the genus, as discussed above.

Applicants respectfully submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully submit that describing a genus of

polynucleotides in terms of physico-chemical properties (e.g., a % sequence identity or stringent hybridization to an exemplary nucleic acid or polypeptide, e.g., SEQ ID NO:1 or SEQ ID NO:2) and function (e.g., encoding a polypeptide having amylase activity) satisfies the written description requirement of section 112, first paragraph. Because the USPTO guidelines recognize that written description is met for a genus of nucleic acids (probes) described by structure, a physico-chemical property and a defined function, the genus of claimed polynucleotides meet the written description requirements of section 112. Applicants respectfully submit that the claims as amended meet the written description requirement under 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §102(b)

*Tachibana*

Claims 1, 2, 11, 15 to 16, 29, 47, 48, 74 to 83, 86, 92, 101 to 106 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachibana, et al., J. Ferment. Bioeng. 1996, vol. 82(3):224-232; GenBank Accession No. O33476, Jan. 1998 ("Tachibana").

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The instant amendment addresses this issue. For example, amended claim 1 is directed to nucleic acids comprising, inter alia, sequences having at least 90% sequence identity to SEQ ID NO:1. Amended claim 2 is directed to nucleic acids comprising, inter alia, sequences that hybridize under specific conditions of high stringency to SEQ ID NO:1, and having at least 90% sequence identity to a sequence as set forth in SEQ ID NO:1. Amended claim 29 is directed to nucleic acids comprising, inter alia, sequences encoding a polypeptide having an amino acid sequence having at least about 95% sequence identity to a sequence as set forth in SEQ ID NO:2.

The cited Genbank reference of "result 4" shows the amylase protein sequence taught by Tachibana to have 91.4% query match and a 90.6% best local similarity to SEQ ID NO:2 of the instant invention. The cited Genbank reference of "result 5" shows the amylase-encoding nucleic acid sequence taught by Tachibana to have 76.5% query match and an 86.0% best local similarity to

SEQ ID NO:2 of the instant invention. The cited Genbank reference of "result 6" shows the amylase-encoding nucleic acid sequence taught by Tachibana to have 76.5% query match and an 84.9% best local similarity to SEQ ID NO:2 of the instant invention.

Accordingly, because Tachibana is not a single prior source that contains each and every limitation of the invention as claimed in the amended claims, the rejection under 35 U.S.C. § 102 can be properly withdrawn.

## CONCLUSION

Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing attorney docket no. 564462006000. Please credit any overpayment to this account.

If the Examiner believes a telephonic conference would expedite prosecution of this application, please telephone the undersigned at (858) 720-5133.

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Respectfully submitted,

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